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FAX TRANSMISSION**DATE:** November 22, 2006**PTO IDENTIFIER:** Application Number 10/581,293

Patent Number

Inventor: Ehrhardt et al**MESSAGE TO:** US Patent and Trademark Office - **MS - PCT****FAX NUMBER:** (571) 273-8300**FROM:** CONNOLLY BOVE LODGE & HUTZ LLP

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PHONE: (302) 658-9141**Attorney Dkt. #:** 12810-00252-US**PAGES (Including Cover Sheet):** 14**CONTENTS:**
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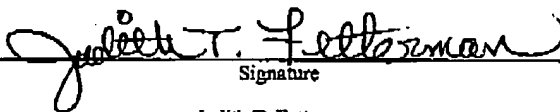
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Docket No.: 12810-00252-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Thomas Ehrhardt et al.

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Application No.: 10/581,293

Confirmation No.: N/A

Filed: June 1, 2006

Art Unit: N/A

For: **CLP-PROTEASE AS TARGET FOR
HERBICIDES**

Examiner: Not Yet Assigned

**TRANSMITTAL OF INTERNATIONAL PRELIMINARY REPORT ON
PATENTABILITY**

MS PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants enclose herewith the International Preliminary Report on Patentability.

Applicants believe no fee is due with this communication. However, if a fee is due, the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 03-2775, under Order No. 12810-00252-US, from which the undersigned is authorized to draw.

Respectfully submitted,

By 

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 0000055117		FOR FURTHER ACTION		See Form PCT/PEA416
International application No. PCT/EP2004/013555		International filing date (day/month/year) 30.11.2004	Priority date (day/month/year) 02.12.2003	
International Patent Classification (IPC) or national classification and IPC INV. C12Q1/37 C07K14/415 G01N33/573 G01N33/569				
Applicant BASF AKTIENGESELLSCHAFT et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 11 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in Item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 29.09.2005		Date of completion of this report 18.05.2006		
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Jacques, P Telephone No. +49 89 2399-6934 		

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**International application No.
PCT/EP2004/013555**Box No. I Basis of the report**1. With regard to the **language**, this report is based on

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-52 as originally filed

Sequence listings part of the description, Pages

1-33 as originally filed

Claims, Numbers

1-26 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify):*
- ☐ any table(s) related to sequence listing *(specify):*

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify):*
- ☐ any table(s) related to sequence listing *(specify):*

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**International application No.
PCT/EP2004/013555**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 21-25 (partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*).

☒ no international search report has been established for the said claims Nos. 21-25 (partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**International application No.
PCT/EP2004/013555**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Yes: Claims	2,7-9,11-12,19-25
	No: Claims	1,3-6,10,13-18,26
Inventive step (IS)	Yes: Claims	21-25
	No: Claims	1-20,26
Industrial applicability (IA)	Yes: Claims	1-26
	No: Claims	

2. Citations and explanations (Rule 70.7):**see separate sheet**

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Re Item III**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The subject-matter of claims 21 to 25 relates to the use of a compound identified by any one of the methods as claimed in any of claims 10-18 and/or 20 for controlling undesired vegetation, for regulating the growth of plants or in a method for the preparation of an agrochemical composition wherein the said compounds are defined as having herbicidal or growth-regulatory activity. However no technical features characterizing the said compounds (e.g. structures), which would permit the skilled person to unambiguously identify them, are given in claims 21-25 which therefore lacks clarity (Art. 6 PCT). Thus, a meaningful search over the whole of the claimed scope was impossible. Only those compounds clearly and unambiguously defined by technical features, i.e. structural features have been searched.

Thus claims 21-25 have been searched only insofar as to compounds as defined in claim 26.

An opinion with regard to novelty, inventive step and industrial applicability is thus given only in relation to those part of the above mentioned claims which have been searched, namely those parts relating to the above mentioned compounds.

Re Item V**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The following documents D are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: DATABASE EMBL [Online] retrieved from EBI Database accession no. AB022327, q9xj36, XP002279219 -& NAKABAYASHI KAZUMI ET AL: 'Identification of clp genes expressed in senescing Arabidopsis leaves' PLANT AND CELL PHYSIOLOGY, vol. 40, no. 5, May 1999 (1999-05), pages 504-514,
- D2: DATABASE EMBL [Online] retrieved from EBI Database accession no. AB022330, Q9XJ35 XP002279220 -& NAKABAYASHI KAZUMI ET AL: 'Identification of clp genes expressed in senescing Arabidopsis leaves' PLANT

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- AND CELL PHYSIOLOGY, vol. 40, no. 5, May 1999 (1999-05), pages 504-514,
- D3: DATABASE EMBL [Online] retrieved from EBI Database accession no. ak118523, q9fn42 XP002279221 -& KOTANI ET AL.: 'Structural analysis of Arabidopsis thaliana chromosome 5.II. Sequence features of the regions....' DNA RES., vol. 4, 1997, pages 291-300,
- D4: WO 03/008440 A (PATTON DAVID ANDREW ;SYNGENTA PARTICIPATIONS AG (CH); ASHBY CARL S) 30 January 2003 (2003-01-30)
- D5: HUANG C ET AL: 'The Chlamydomonas chloroplast clpP gene contains translated large insertion sequences and is essential for cell growth.' MOLECULAR & GENERAL GENETICS: MGG. GERMANY 25 JUL 1994, vol. 244, no. 2, 25 July 1994 (1994-07-25), pages 151-159,
- D6: SHIKANAI TOSHIHARU ET AL: 'The chloroplast clpP gene, encoding a proteolytic subunit of ATP-dependent protease, is indispensable for chloroplast development in tobacco' PLANT AND CELL PHYSIOLOGY, vol. 42, no. 3, March 2001 (2001-03), pages 264-273,
- D7: CLARKE ADRIAN K ET AL: 'Inactivation of the clpP1 gene for the proteolytic subunit of the ATP-dependent Clp protease in the cyanobacterium Synechococcus limits growth and light acclimation' PLANT MOLECULAR BIOLOGY, vol. 37, no. 5, July 1998 (1998-07), pages 791-801,
- D8: ADAM ZACH ET AL: 'Chloroplast and mitochondrial proteases in Arabidopsis. A proposed nomenclature' PLANT PHYSIOLOGY (ROCKVILLE), vol. 125, no. 4, April 2001 (2001-04), pages 1912-1918.
- D9: HEINE, HAROLD W. AND BROOKER, ANNE C.: 'The isomerization of aziridine derivatives. VI. The rearrangement of some 2-(1-Aziridinyl)quinoxalines' JOURNAL OF ORGANIC CHEMISTRY, vol. 27, 1962, pages 2943-2944,
- D10: DATABASE REGISTRY STN; 29 May 2001 (2001-05-29),

2. The subject-matter of claim 1 is not new (Art. 54 EPC).

2.1 Document D4 discloses nucleotides sequences isolated from Arabidopsis thaliana that code for proteins essential for plant growth and development. The said proteins are exploited by recombinantly expressing them and using them in vitro or in vivo screening assays to identify compounds that interact with or inhibit the proteins

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activity and are therefore potential herbicides (see abstract; p.18, IV; p.21, point VI). Document D4 discloses that one of the above mentioned protein is the regulatory subunit of Clp protease with ATPase activity in *Arabidopsis thaliana* (AtClpC) (see table 5, gene 62837, sequences 81-82).

It is well known from the art (see D8, p. 1912, right-hand column, second paragraph and p.1913, right-hand column, the "Clp Proteases" section) that the said regulatory subunit associates with a small subunit containing the proteolytic active site (ClpP) to form an active Clp-protease.

Thus, D4 already discloses that the Clp-protease is essential for plant growth. Furthermore, the regulatory subunit alone does not present any enzymatic activity. This activity is only present when associated with the proteolytic subunit to form the enzyme. It is thus clear that the screening assays for identifying herbicides based on the inhibition of the enzyme activity (p.20, I.10-25; p.21, point IV) disclosed in D4 inevitably involves the use of an active Clp-protease and not only the AtClpC subunit. Thus, the subject-matter of claim 1 is anticipated by D4.

- 2.2 The applicant argued that document D4 is concerned with a method for identifying herbicides wherein chloroplast encoded Clp proteases are used and has filed several abstracts corresponding to cited references in D4. Applicant argued that the present invention relates to a method for identifying herbicides wherein a nuclear encoded Clp-protease is used.

Clp-proteases are composed of a proteolytic subunit, ClpP, and a regulatory subunit, ClpC. Adam et al., *Biochimie* 82 (2000) 647-654, cited in D4 and filed by the applicant, discloses that both subunits can be nuclear encoded (p. 649, section 3.2) and then migrate to the chloroplast. The other citations disclose that the regulatory subunit is chloroplast encoded. It is also clear from the other citations and from the description p.8, I. 25-27 that the ClpP subunits are nuclear encoded.

Thus, as explained above (see point 2.1), the method for identifying herbicides as disclosed in D4 necessarily uses a Clp-protease having at least a ClpP subunit being nuclear encoded.

It is not clear from the subject-matter of claim 1 if the term Clp-protease encompasses both subunits or only the ClpP subunit. From the wording of claim 2 ("wherein the Clp-protease is") it would however appear that only the ClpP subunits fall under the term Clp-protease.

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In the view of this, the subject-matter of claim 1 is anticipated by D4 wherein the Clp-protease comprises necessarily a ClpP subunit which is nuclear encoded.

NB : Should claim 1 encompass both subunits, i.e. a Clp-protease having nuclear encoded ClpC and ClpP subunits, the subject-matter of claim 1 would appear to be new as D4 does not specifically disclose a Clp-protease having two nuclear encoded subunits. Claim 1 would however not involve any inventive activity (Art. 33(3) PCT) as D4 suggests such a combination (see above mentioned citation Adam et al.).

- 2.3 Additional note: it would appear that the subject-matter of claim 1 would also not involve an inventive step (Art. 56 EPC).

The applicant states in the description, p. 48, l. 14-18 that he showed for the first time and in a surprising manner that Clp protease is essential for plants and that reducing expression leads to damage (chlorosis and growth retardation), thus demonstrating the suitability of Clp-proteases as target for herbicides.

It would however appear that the said statement is wrong. As mentioned above, document D4 already defines the Clp-protease as essential for plant growth. Documents D5 (abstract) discloses that Clp gene is essential for cell growth in algae, D6 (abstract) discloses that Clp is indispensable for cell survival in Tobacco, D7 (abstract) teaches that ClpP1 protease is essential for growth of cyanobacterium.

Thus, these documents clearly teach the concept that Clp proteases are essential for plants and that reducing their expression leads to damage. Thus, the skilled man would have drawn the same conclusion as mentioned in the description, namely that the said proteases are suitable targets for herbicides.

In the view of the said documents, the subject-matter of claim 1 would not involve an inventive step in the sense of Art. 56 EPC.

3. For the same reasons as mentioned under above point 2, the subject-matter of independent claims 10 and 17 and dependent claims 13-16 and 18 are also not new (Art. 54 EPC).
4. The subject-matter of claims 3, 4, 5 and 6 are not new (Art. 54 EPC). Document D1 discloses a nucleic acid sequence of Arabidopsis thaliana (Acc. No AB022327) and the protein sequence encoded by the said sequence (Acc. No:

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Q9XJ36) being, respectively, functional equivalents of SEQ ID No. 3 (with 71 % identity) and SEQ ID No: 4 (with 76 % identity) (see abstract and sequence alignment).

Document D2 discloses a nucleic acid sequence of *Arabidopsis thaliana* (Acc. No AB022330) and the protein sequence encoded by the said sequence (Acc. No: Q9XJ35) being, respectively, functional equivalents of SEQ ID No. 11 (with 74 % identity) and SEQ ID No: 12 (with 71 % identity) (see abstract and sequence alignment).

Document D3 discloses a nucleic acid sequence of *Arabidopsis thaliana* (Acc. No AK118523) and the protein sequence encoded by the said sequence (Acc. No: Q9FN42) being, respectively, functional equivalents of SEQ ID No. 17 (with 75 % identity) and SEQ ID No: 18 (with 82 % identity) (see abstract and sequence alignment).

5. The subject-matter of dependent claims 2, and 11-12 appears to be new (Art. 33(2) PCT) as D4 does not disclose a specific Clp-protease as disclosed in the said claims. The said claims do however not meet the requirements of Art. 33(3) PCT as all the subunits selected are well known in the art.
6. As the particular combination of features of independent claims 7 (with the limitation mentioned under point 2 in Item VIII), 8, 9 and 19,20 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 54 EPC).
However, the said claims are not inventive (Art. 56 EPC) as it would be obvious for the skilled man to put the known sequences of claims 3-5 in an expression cassette and the said cassette in a vector to generate a transgenic non human organism or to bind the said sequences, cassette, vector or organism to a support and to use the said support in the known method of claim 10.
7. As the particular combination of features of independent claim 21 (with the restriction mentioned under above Item III) is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 33(2) PCT).
Moreover, it would appear that the said claim involves an inventive step in the sense of Art. 33(3) PCT as none of the cited prior art documents disclose the use of any of

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the compounds having formula (I), (II) or (III) as disclosed in claim 26, for controlling undesired vegetation and/or regulating the growth of plants.

The same reasoning applies to claims 22 to 25 (with the restriction mentioned under above Item III) which are new (Art. 33(2) PCT) and inventive (Art. 33(3) PCT).

8. The subject-matter of claim 26 is not new (Art. 33(2) PCT) as document D9 discloses the compound of the formula (II) (see p.2944, compound Ia.) and document D10 discloses compound of the formula (III) (see the disclosed structure on the said document).

Additional note : it would appear that compound of the formula (I) is not anticipated by the prior art.

9. Claims 9, 14 and 15 refer to a transgenic organism expressing a Clp-protease. It would appear that the said transgenic organism encompasses human beings and thus most national and regional jurisdictions would consider such methods as being contrary to morality.

Re Item VII**Certain defects in the international application**

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents to D1 to D10 is not mentioned in the description, nor is/are this/these document/s identified therein.

Re Item VIII**Certain observations on the international application**

1. Unclearness (Art. 6 PCT) arises in the present claims since the term Clp-protease is used to define either the whole Clp-protease (proteolytic subunit ClpP and regulatory subunit ClpC-see above point 5) or the proteolytic subunit ClpP alone. Thus, to avoid any confusion, claims 2-5, 11-12 should be directed to the ClpP subunit of the Clp-protease.

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2. The subject-matter of claim 7 is not clear (Art. 6 PCT) as the elements of embodiment b) are not defined by technical features characterizing the said elements, thus putting an undue burden on others seeking to determine the extend of the protection.
Furthermore, it is unclear (Art. 6 PCT) how an expression cassette can work if only additional functional elements are present. Thus, examination has been carried out only with regard to embodiments a) and c).
3. Document D5 teaches that ClpP1 is the only isomer encoded within the plastid genome (p.1913, right-hand column, section "Clp proteases), whereas the present application states that the said isomer is nuclear encoded.
4. The subject-matter of claims 9 should refer back to claims 3,4 and 5 and not 4, 5 and 6 (Art. 6 PCT).
5. The word "has" to be found in the expression "of has at least" in parts c) of claims 3, 4 and 5 should be deleted for clarity reasons (Art.6 PCT).
6. The incorporation of prior art by reference is not allowed as the international application should be self-contained (see further PCT Guidelines, C-II, 4.17). Phrases such as "and incorporated by reference..." to be found e.g. on page 13, line 40, page 15, line 32 and page 17, line 3 contravene said requirement.

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